99-045-1

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August 13, 1999

Docket No. 99-045-1
Regulatory Analysis and Development
PPD, APHIS
Suite 3C03
4700 River Road, Unit 118
Riverdale, Maryland 20737-1238

Re: Comments on Draft Guideline on Good Clinical Practices, VICH Topic GL9, Noted in 64 Fed. Reg. 34764 (June 29, 1999); Docket No. 99-045-1

Ladies and Gentlemen:

These comments to Docket No. 99-045-1 are submitted on behalf of the Association of Veterinary Biologics Companies (AVBC), an international association of manufacturers of veterinary biologics products licensed by the U.S. Department of Agriculture. Among the 26 USDA licensee members of AVBC are nearly all the major manufacturers and many smaller firms. Any guideline adopted by the USDA's Animal and Plant Health Inspection Service (APHIS) pursuant to the VICH Draft Guideline on Good Clinical Practices may have a significant impact on the members of AVBC.

The leadership of APHIS and the other participants in the VICH program are to be complimented for their efforts to undertake this particular topic. Clinical research is very expensive, and it is in everyone's interest to conduct the studies properly the first time and in a manner that will be acceptable to regulatory authorities around the world.

As noted in the Fed. Reg. notice, the principles in the draft GCP guideline are already contained in 9 CFR § 103.3 and VS Memorandum 800.84. The GCP guideline, however, requires over 27 pages to set forth the principles APHIS states in less than one page of the Code of Federal Regulations. The guideline itemizes all the concerns and considerations, rather than sticking with principles. The guideline requires the documentation of many more elements than § 103.3. The scope and style of § 103.3 and Memo 800.84 recognize the value of flexibility, and this should be retained.

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As detailed below, there are many points on which the GCP draft guideline is not appropriate for the conduct of clinical studies of veterinary biologics. We recommend that VICH develop a separate GCP guideline for biologics.

The philosophy of the GCP document is based on the current regulatory scheme in some EU countries and FDA's Center for Veterinary Medicine. These may be laudable principles, but much of the guideline applies only to pharmaceutical and feed additive products. However, if APHIS were to adopt this guideline, there would be endless debates regarding whether specific sections apply to biologics, and, if so, how. Veterinary biologics studies have unique requirements which justify the use of a specific guideline for clinical studies. Trying to shoehorn APHIS- and FDA-regulated products into the same guideline would represent a major change in regulatory policy and one which will only blur the separation of the two agencies and their regulatory responsibilities. AVBC members are more than willing to work with APHIS in any way to develop specific guidelines, but the association is opposed to adopting guidelines in which biologics are little more than an afterthought.

The veterinary biologics industry in the United States developed separately from the pharmaceutical industry, and it has evolved into arguably the premier animal health product system in the world. The U.S. veterinary biologics industry is distinguished by the large number and diversity of companies, which has resulted in fierce competition and the availability of a wide range of safe and effective products at a reasonable cost to consumers.

We are concerned that these guidelines will add to the costs of our products, which will have to be passed on to the consumer in an ever upwardly spiraling trend -- with little or no added benefit. Furthermore, potentially useful products will not be produced if the expected market is too small to provide a return at competitive prices.

On the other hand, what added benefits will accrue from the use of this guideline? A GCP guideline designed for veterinary biologics clinical trials will help eliminate the errors that lead to the failure or rejection of a study, but a protocol designed to study medicated feed additives will probably produce a great deal of useless data. Generating such data would simply be a waste of money and animals.

We must examine proposed procedures from the perspective: *Is it necessary?* There is much data that it would be interesting or helpful to have, but sound scientific and regulatory judgment must limit the requirements to the bare necessities. To the extent that the principles contained in the CPG guideline have been adopted by the EU, the track record of benefits is dubious. See, e.g., the attached article from Animal Pharm, July 16, 1999, summarizing recommendations to simplify the EU registration process for veterinary products.

Another concern with the GCP guideline is that it could represent the agency's abandonment of a principle that has made the 9 CFR program so successful -- that is the agency's regulatory philosophy of flexibility in the method of compliance with requirements. APHIS's approach has been vindicated by recent regulatory reform initiatives. Throughout the 1990s, the federal government's regulatory philosophy has emphasized flexibility over rigidity and results over bureaucracy. This is the spirit of Vice President Gore's Reinventing Government initiative, the Small Business Regulatory Enforcement Fairness Act administered by SBA, and, by analogy, the FDA Modernization Act. This principle needs to be clearly articulated in APHIS's version of the GCP guideline.

There are several statements in APHIS's Federal Register notice that have raised questions.

a. The notice includes a statement that this draft guideline reflects current APHIS thinking. We hope that this is not the case, unless we fail to understand how the agency intends to use the documents produced through the VICH process. As noted, AVBC supports the current principles contained in 9 CFR and VS Memorandum 800.84, and the association believes that the principles enunciated in Sec. 2 of the GCP guideline are, by and large, consist with the current program. However, the detailed lists of criteria, the extensive recordkeeping and reporting requirements, and duplicative supervision and oversight of studies and data analysis are certainly not consist with current practice.

b. This leads to the question, has APHIS identified any changes that would occur in the agency's preferences for study design, conduct, or reporting if this guideline were adopted? If so, has the agency developed a rationale for such changes?

c. The Notice also states that the guideline will be used as the basis for approval of shipment of experimental products. The intend of this statement is not clear, because the sponsor would be expected to ship the product pursuant to § 103.3 for the purpose of conducting the study covered by the guideline.

AVBC concluded that a separate guideline is needed for veterinary biologics studies after a review of the VICH GCP proposal. The following sections of this letter illustrate several of the inappropriate or inconsistent provisions in the guideline as proposed.

1. Sec. 2.7. states that experimental products should be prepared in accordance with the concepts of GMP. This statement needs to be clarified; the important consideration for the regulatory authority should be the sponsor's assurance that the experimental product can be duplicated in the final product. For APHIS-regulated products, the guideline should state that the experimental products will be prepared in accordance with the manufacturing requirements of 9 CFR.

2. Sec. 3.2 identifies a long list of responsibilities that the investigator has for the management of the study. Many of them cannot be documented and, thus, must be advisory. Several of the items represent needless documentation:

Sec. 3.2.13. requires the owners' informed consent, but that will be implicit in most circumstances.

Sec. 3.2.28, requiring a contact log, is not needed.

Sec. 4.2.15. appears to require a study report on each animal given an investigational product.

3. Secs.3.2.17 - 3.2.20., covering the handling of investigational and control products, will have -- at most -- limited applicability to studies of veterinary biologics.

4. Sec. 4.2.16. requires a quality audit. This is not defined or explained.

5. We anticipate that the effect of the protocol checklist proposed in Sec. 6.3 would be that the sponsor will have to routinely identify to the regulatory authority the elements that are not applicable to its study. The sponsor may have to

overcome a presumption that all elements apply, and there may be the prospect of a lengthy negotiation with the regulatory authorities before the start of each study over which elements apply.

There is a vast reservoir of scientific expertise to draw on in the Center for Veterinary Biologics to make scientific decisions. The decisions on study design, analysis, and reports should be grounded in scientific judgment not bureaucratic checklists. We suggest that neither CVB nor the industry has the resources to enter into extended debate on the appropriateness of the many elements on this list.

6. Sec. 6.3.8.4. requests the identity of the experimental unit. This is not defined.

7. Sec. 6.3.11., on animal management and housing, would seldom be applicable to field studies.

8. Sec. 6.3.13., on controls, feed, water, etc., appears to be applicable mostly to pharmaceutical products.

9. Sec. 1.24 and 4.1 both state that the sponsor "is liable for the veterinary product under investigation." We do not know what that means; we certainly expect that it does not mean to imply a USDA waiver of federal preemption of state product liability laws. It could be revised to read that the sponsor is "responsible" for the product, i.e., it is the sponsor's job to provide the product and assure that it meets specifications.

10. Sections 3 and 5 presume that it is always necessary to have an independent monitor. This does not seem to be warranted. In a small company, the sponsor and investigator or the sponsor and the monitor are the same. If the study is properly designed and documented, there will be an adequate record for the regulators to review (audit) without 3 independent actors. This is another topic for potential debate with reviewers.

This long list of concerns stems in part from the fact that very little of the U.S. biologics industry had an opportunity to participate as the guideline was being put together in the VICH working group. The document needs substantial further discussion of how to capture the safety, efficacy, and quality requirements of 9 CFR. AVBC welcomes the opportunity to work with APHIS and VICH to develop an appropriate guideline covering studies of veterinary biologics. But at the moment, AVBC recommends that

APHIS refuse to support the finalization of the draft GCP guideline if it would apply to veterinary biologics development in the U.S.

Please do not hesitate to contact us with any questions or comments on this letter.

Yours truly,

LUMAN, LANGE & WHEELER

John W. Thomas

JT/pc
cc: Dr. Richard E. Hill, Jr.
Dr. David Espeseth
AVBC Members

EU vet legn endangers food supply

EU legislation governing veterinary products is endangering the food supply and threatening animal health and welfare. Regulations governing the registration and use of veterinary products in the EU are not only detrimental to consumers and the European animal population, but also damaging to the animal health industry. The industry is also arguing that innovative veterinary medicines will only continue to reach the European market if the animal health industry is no longer subjected to the "unbearable requirements combined with legal uncertainty".

These were amongst the conclusions of a conference set up to examine medicine availability in July. Organised by the representative bodies of the farming, veterinary, pharmacy and animal health industries, the event resulted in a number of proposals to improve veterinary medicines availability within the EU which were sent to the Commission, the EMEA and the European Council.

There were unanimous calls for the simplification of registration procedures for existing and new products without reducing consumer protection. Delegates also asked for the technical requirements of the marketing authorisation procedures to be interpreted more realistically and for new requirements not to be applied automatically to some older products, which have already been proven to be safe.

The conference also considered that, in general, MRLs should be applicable to all food-producing species and that, unless expressly specified, an MRL should be established for two target tissues only.

Considering off-label use in food-producing animals, it was agreed that an urgent review of the provisions governing such use was needed, to better reflect the daily needs of veterinarians. Participants agreed that the use of products without an MRL in food producing animals should only be authorised in exceptional circumstances and accompanied by a sufficient withdrawal period. With regard to marketing authorisation requirements and procedures, an overall simplification of European procedures was called for.

EU beef trade surplus lower in 1998

The EU imported 386,700 tonnes of beef (carcass weight equivalent, including live animals) from third countries in 1998, down almost 10% from the 429,000 tonnes imported in 1997, reports the UK's Meat and Livestock Commission.

The main importer, the UK, imported 137,800 tonnes, 13.3% below its 1997 total of 158,900 tonnes. German imports were down by 2.7% to 78,300 tonnes, and Italian imports fell by 3.9% to 60,800 tonnes. Belgium, Denmark, Sweden and Portugal all increased their imports of beef from third countries. Preserved or prepared products accounted for around 33% of beef imports (127,000 tonnes), while frozen beef represented 32%, and fresh or chilled products 27%.

EU beef exports to third countries fell by 26.8% to 769,200 tonnes in 1998, according to Eurostat-Cometext figures. Ireland was the only EU member state to increase its beef exports in 1998, recovering a number of its former Middle Eastern markets during the year (Animal Pharm No 407, p 8), a factor which helped boost sales by 7.8% to 267,400 tonnes. However, the UK remained Ireland's main beef export market. Germany, the second largest exporter of the year, sold 171,900 tonnes to third-country markets, a drop of 31% on its 1997 total of 249,200 tonnes.

The EU's trade in beef during the year resulted in a trade surplus of 382,500 tonnes.

EU lifts Belgian dairy restrictions

The EU has authorised the lifting of most of the restrictions imposed on Belgian dairy products after the dioxin crisis (Animal Pharm No 423, p 1), reports Agra Europe. The EU Standing Veterinary Committee (SVC) approved a proposal to ease the controls after tests on produce from over 280 Belgian dairy farms showed dioxin levels were below the approved limit. Only nine farms are required to undergo further testing for dioxin contamination. The SVC approved the proposal by nationally weighted qualified majority, with only the Danish and Austrian representatives voting against the motion.

The SVC has also removed the requirement for Belgian dairy products, either intended for the domestic market or for export, to carry a veterinary certificate guaranteeing that the milk comes from a non-contaminated farm. The SVC has also set a maximum fat content level of 2% for all dairy products, which means that all products with dairy fat content of less than 2% are considered safe.

Meetings

[illegible] Associations (FECAVA) and France's national small animal veterinary association (CNVSPA), the ***26th World Veterinary Congress (Mondial Vet 1999)*** will take place from September 23rd-26th 1999 at the Palais des Congrès in Lyon, France (see this issue, p 13). The congress will include presentations by over 150 speakers, with simultaneous translation into English, French, Spanish, Italian and German. Throughout the conference, 16 halls will be in continual use, hosting a variety of conferences on topics including emerging infections, buiatrics and resistance to antibacterial drugs. The congress will also include a commercial exhibition covering 3,000m^2 floor space, featuring over 160 commercial exhibitors. For further details, contact: Mondial Vet 1999, CNVSPA, 40 rue de Berri, 75008 Paris, France. Tel: +33 1 53 83 91 60; fax: +33 1 53 83 91 69; e-mail: *mondialvet@aol.com;* website: http://www.mondialvet99.org